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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,023	06/28/2001	Vladmir R. Muzukantov	PENN-0749	7329

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,023	MUZUKANTOV ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/06/04 has been entered.

2. Claim 9 is pending and under examination.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bowes et (Neurology 1995) in view of Mulligan et al (Amer. Pathol. 1993), or Panes (Amer. Physiol. 1995), and Muzykantov et al (BBA 1986), Runge et al or Torchilin et al (all of record).

Bowes *et al* teach that administration of an anti-lCAM-1 mAb and the drug tPA to rabbits prevents leukocyte adhesion and increases post ischemic duration at which thrombolytic therapy remains effective in cerebral ischemia and reperfusion (especially Abstract). Bowes *et al* also teach that administration of tPA alone improves neurologic outcome in models of ischemia, but that obstacles exist to therapy, and further that reperfusion may also result in additional neurologic damage as ischemic tissue is reoxygenated (abstract in particular).

The claimed invention differs from the Bowes *et al* teachings only by the recitation of conjugate and a nono-internalizable antibody or ICAM-1 in claim 9.

Panes *et al* teach that ICAM-I is constitutively expressed on vascular endothelium of the rat and there are significant regional differences in magnitude of expression.

Mulligan *et al* teach anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature (see table I, and page 1744, 2nd col., 1st ¶ in particular), i.e., non-internalizable anti-ICAM-1 mAb 1A29, challenged with pro-inflammatory agents, and that blocking of ICAM-1 is tissue protective in a manner in which neutrophil recruitment is attenuated. Mulligan et al further teaches that the radiolabeled anti-ICAM-1 (1A29) antibodies were intravenously injected (page 1741, under in vivo ICAM-1 quantification, in partricular).

Runge *et al* teach the thrombolytic drug tPA can be efficiently directed to the site of a thrombus by conjugation, i.e., chemical modification, to an anti-fibrin monoclonal antibody, resulting in both more potent and more selective thrombolysis (especially Abstract).

Torchilin *et al* teach that targeted accumulation of thrombolytic enzymes in the region of thrombus location can be achieved by their coimmobilization with specific antibodies (especially Abstract). Torchilin et al further teach drawbacks in administration of tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis (especially page 322) may be resolved by the use of antibody-immobilized tPA.

Muzykantov *et al* teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation.

Given the teachings of Mulligan *et al* that anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, it would be immediately apparent to one skilled in the art that the antibody is non-internalizable.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the tPA to a mAB (such as 1A29) as taught by Torchilin et al, Runge et al or Muzykantov *et al* targeting fibyrolytic agents or for other molecules recognizing mAb specific for target molecules on vascular endothelium using chemical modification as taught by Muzykantov et al or Runge et al and further, substitute the resultant conjugate for the anti-ICAM-1 mAb in the composition of Bowes et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because ICAM-1 is constitutively expressed on vascular endothelium as taught by Panes *et al.* or Mulligan et al and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al.

Applicant' arguments submitted on 8/06/2004 have been considered but found not persuasive.

Applicant traveres the rejection on the ground that Mulligan's et al experiments relating to accumulation in the pulmonary vasculature are not indicative in any way of internalization or lack of internalization of an antibody into endothelial cells. Applicant submits that Mulligan's et al experiments in no way provided information as to whether the label was inside or out side the cell. Applicant further argues that the cobination of references still provides no reasonable expectation that a fibrinolytic or anticoagulant agent, when conjugated to a non-internalized antibody would remain therapeutically active for prolonged periods in the lumen, particularly when it was well known in the art that anticoagulants and fibrinolytics undergo inactivation and elimination in the bloodstream.

While Mulligan et al teachings is silence regarding the antibody internalization per se, it would be immediately apparent to one skilled in the art that the accumulation of the antibody in the pulmonary vasculature is due to non-internalization of said antibody. Regarding, the lack of reasonable expectation that a fibrinolytic or anticoagulant agent when conjugated to a non-internalized antibody would remain therapeutically active for prolongedperiods in the lumen. Applicant argues that the prior art is not suggestive of the desirability of a conjugate of a non-internalizable antibody to ICAM-1 to an anti-thrombotic agent which prolongs length of time of the anti-thrombotic agent in the bloodstream was well-established problem.

While it is true that anticoagulants and fibrinolytics undergo inactivation and elimination in the bloodstream, However, the teachings of Torchilin *et al* pertaining to the drawbacks in administrating the thrombolytic tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis may be resolved by the use of antibody and the teachings of Runge *et al* indicating success in directing the thrombolytic drug tPA to the site of a thrombus by conjugation resulting in both more potent and more selective thrombolysis. The combined reference teachings solved a similar problem such would led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

Applicant further agrues that the prior does not provide reasonable expectation of success as required by MPEP 2143.02 that a conjugate of a non-internalizable antibody to ICAM-1 to an anti-thrombotic agent will remain active when maintained for prolonged periods in the bloodstream, an area where stability of such agents is problematic.

In contrast to applicant's arguments, there was clear teaching and therefore expectation of success to conjugate of the antibody to ICAM-1 to an anti-thrombotic agent as the claimed invention.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
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August 25, 2004

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